# The feasibility of withdrawing canakinumab in paediatric colchicine-resistant familial Mediterranean fever patients

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*Received on March 12, 2021; accepted in revised form on July 12, 2021.*

*Clin Exp Rheumatol 2021; 39 (Suppl. 132): S118-S123.*



**Key words:** canakinumab, colchicine resistance, familial Mediterranean fever

*Competing interests: none declared.*

**ABSTRACT**

**Objective.** *To determine the feasibility of withdrawing canakinumab (CAN) in a large cohort of paediatric patients with colchicine-resistant familial Mediterranean fever (crFMF).*

**Methods.** *This retrospective observational cohort study included paediatric crFMF patients that received CAN treatment for ≥6 months. Patient data were recorded at treatment onset (baseline), and at 1, 3, 6, 12, 18, and 24 months after initiation of treatment.*

**Results.** *The study included 114 patients that were followed-up for 2736 person-months. During the 24-month follow-up period, the CAN dose interval remained unchanged in 44 patients. The dose interval was extended in 58 patients within a median 6 months (range: 3–18 months) of treatment initiation. In all, 4 of these 58 patients had a new attack of crFMF after the dose interval was extended. CAN was withdrawn in 12 patients (in 5 at month 12 month and in 7 at month 18), of which 2 had a new attack within 3 months of withdrawal. In these 2 patients CAN was re-initiated with a dose interval of 8 weeks. The remaining 10 patients in which CAN was withdrawn did not report any symptoms throughout the remainder of the 24-month follow-up period. The median attack-free period in those treated with CAN was 669 d (95% CI: 644–696).*

**Conclusion.** *The present findings show that it may be feasible to withdraw CAN or extend its dose interval in paediatric crFMF patients. Based on the present findings, we think that as the quantity of real-life data increases, standard CAN protocols may be developed.*

## Introduction

Familial Mediterranean fever (FMF) is a systemic autoinflammatory disease characterised by recurrent attacks of serositis accompanied by fever, usually lasting 12–72 h (1). FMF is caused by recessively inherited mutations in the *Mediterranean FeVer (MEFV)* gene that encodes pyrin, resulting in overproduction of interleukin (IL)-1β (2). Colchicine is the mainstay of the treatment of FMF, decreasing attack frequency and preventing secondary amyloidosis (3). Although colchicine has dramatically improved the quality of life in the majority of FMF patients, it is unfortunately ineffective in 5–10% of patients with FMF (4). There is no standard definition for "colchicine resistance" in FMF patients. Clinicians agree that patients may be considered colchicine resistant in the presence of ongoing clinical disease activity and inflammation, whereas opinions vary regarding the frequency of attacks required to define patients as colchicine resistant (4, 5).

With the advent of translational research, anti-IL-1 agents have emerged as a new and effective therapeutic approach in colchicine-resistant FMF (crFMF) patients (6-10). There are 3 anti-IL-1 agents available: anakinra, canakinumab, and rilonacept. Anakinra is a recombinant, human IL-1 receptor antagonist, canakinumab (CAN) is a human IgG1 monoclonal antibody directed against IL-1β, and rilonacept is a fully human dimeric fusion protein that binds to the extracellular domains of IL-1α and IL-1β (10). CAN is the only drug approved for FMF by the US Food and Drug Administration (9). The efficacy of CAN in crFMF patients was shown by 2 open-label pilot studies and 1 randomised controlled study (8, 11, 12); however, data regarding drug survival, the dose interval, and optimal dose are inconsistent. One small-scale case series reported that the dose inter-

val could be extended, but long-term results are lacking (13, 14).

The aim of the present study was to determine the feasibility of withdrawing CAN in a large cohort of paediatric crFMF patients.

## Materials and methods

This retrospective observational cohort study included paediatric crFMF patients that were treated with CAN for ≥6 months. Data at baseline, and 1, 3, 6, 12, 18, and 24 months after initiation of CAN treatment, including demographic data, clinical and laboratory features, genetic analysis, treatment response, and adverse events, were obtained from the Paediatric Rheumatology Academy (PeRA)-Research Group (RG) database (15). Patients were diagnosed with FMF according to paediatric FMF criteria (16). Colchicine resistance was defined as the presence of ≥6 attacks per year, ≥3 attacks during a 4-6-month period, elevation of ≥2 acute phase reactants (APRs) during incomplete attacks, or evidence of subclinical inflammation between attacks (5). In the presence of an attack or elevated APRs the CAN dose was gradually increased by 2 mg $kg^{-1}$ every 1 or 2 months until complete remission was achieved. Complete response to CAN was defined as no attacks or signs of subclinical inflammation (normal APR levels during the attack-free period). Partial response was defined as a decrease in the frequency of attacks. Colchicine treatment was continued in all patients along with CAN. The CAN dose interval was extended after complete remission was achieved.

The Physician Global Assessment (PGA) (a visual analogue scale of 0-10, in which 0 indicates no disease activity) was administered at every follow-up visit. All patients were screened for tuberculosis before initiation of CAN treatment. Drug survival was defined as the time from initiation of CAN treatment to withdrawal of CAN (17). The study protocol was approved by the University of Health Sciences Ethics Committee (approval no. B.10.1TKH.4.34.H.GP.0.01/251).

### *Statistical analysis*

Statistical analysis was performed using IBM SPSS Statistics for Windows v. 21 (IBM Corp., Armonk, NY). The study variables were investigated using visual (histograms and probability plots) and analytic methods (the Kolmogorov-Smirnov test) to determine the normality of distribution. Descriptive data are expressed as mean ± SD or median (range), as appropriate. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. The continuous data between the two groups were compared by Mann Whitney U-test. Friedman's test was used to compare continuous parameters not normally distributed and the Wilcoxon test was used to determine the significance of pairwise differences using Bonferroni correction to adjust for multiple comparisons. The attack-free period was determined using the Kaplan-Meier method.

## Results

### *Baseline patient characteristics*

The study included 114 crFMF patients that were followed-up for 2736 person-months. Among the patients, 68 (59.6%) were female and 46 (40.4%) were male. The median age at symptom onset and diagnosis was 30 months (range: 1–154 months) and 62 months (range: 3–173 months), respectively. The median diagnostic delay was 21.5 months (range: 0–136 months). Patients were followed-up a median 82.5 months (range: 7–106 months). The rate of consanguineous marriage among the patients' parents was 36% (n=41). In total, 70 (61.4%) patients had a positive family history of FMF.

**Table I.** Baseline characteristics of the crFMF patients.

| Clinical findings | n (%) |
|---|---|
| Fever | 114 (100) |
| Abdominal pain | 109 (95.6) |
| Chest pain | 41 (36) |
| Arthralgia | 76 (66.7) |
| Arthritis | 45 (39.5) |
| Myalgia | 47 (41.2) |
| Exertional leg pain | 42 (36.8) |
| Prolonged febrile myalgia | 4 (3.5) |
| Erysipelas-like erythema | 47 (41.2) |
| Diarrhea | 23 (20.2) |
| Vomiting | 11 (9.6) |
| Splenomegaly | 16 (14) |
| Headache | 13 (11.4) |
| Amyloidosis | 4 (3.5) |
| Pericarditis | 1 (0.9) |
| **Laboratory findings Median (range)** | |
| CRP, mg $dL^{-1}$* (normal: ≤0.5) | 46.2 (11-83) |
| ESR, mm $h^{-1}$* (normal range: 0-20) | 47 (3-126) |
| SAA, mg $^{-1}$L* (normal: <7) | 89 (2.9-1870) |
| ***MEFV* mutations** | **n (%)** |
| M694V/M64V | 64 (56.1) |
| M694V/M680I | 16 (14) |
| M694I/M694I | 12 (10.5) |
| M680I/V726A | 12 (10.5) |
| M694V/R761H | 2 (1.8) |
| M694V/- | 5 (4.4) |
| M694V/E148Q | 1 (0.9) |
| M680I/M680I | 1 (0.9) |
| M694V/V726A | 1 (0.9) |

*During an attack before initiation of colchicine.

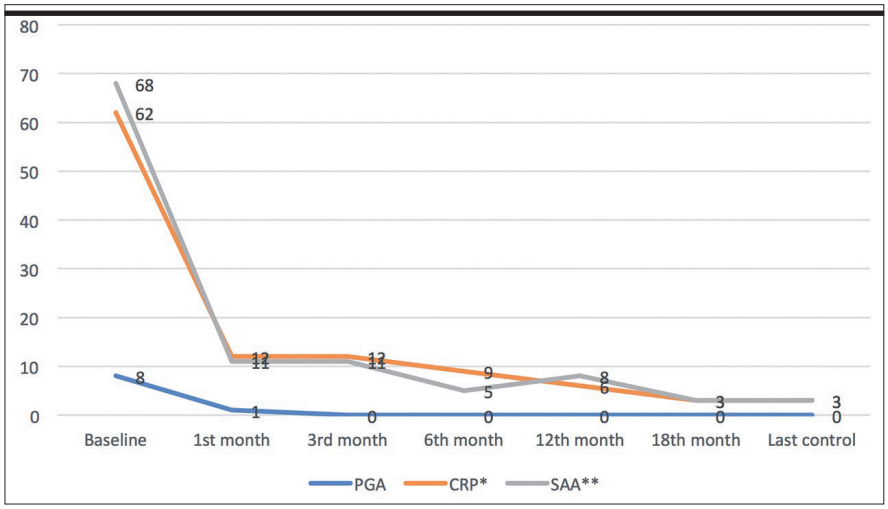


**Fig. 1.** Response to CAN treatment in the crFMF patients.
*Number of patients with elevated CRP.
**Number of patients with elevated SAA.

**Table II.** Response to CAN treatment in the crFMF patients.

| | Baseline (n=114) | 1st month (n=114) | 3rd month (n=114) | 6th month (n=114) | 12th month (n=114) | 18th month (n=114) | 24th month (n=114) |
|---|---|---|---|---|---|---|---|
| **PGA*** | 8 (5-10) | 1 (0-10) | 0 (0-5) | 0 (0-5) | 0 (0-3) | 0 (0-5) | 0 (0-3) |
| **CRP*** | 16.2 (11-31) | 0.65 (0.02-58.6) | 0.2 (0-15.8) | 0.7 (0-68) | 0.5 (0-24.9) | 0.3 (0-41) | 0.3 (0.16.1) |
| **SAA*** | 89 (2.9-1870) | 3.9 (0-17) | 4 (0-23) | 3.3 (0-70) | 3.6 (0-152) | 3 (0-42) | 3 (0-24) |
| **CAN dose interval (weeks)** | 4 (4-8)<br>4 weeks in 94<br>8 weeks in 20 | 4 (4-8)<br>4 weeks in 94<br>8 weeks in 20 | 4 (4-8)<br>4 weeks in 94<br>8 weeks in 20 | 6 (4-8)<br>4 weeks in 66<br>6 weeks in 21<br>8 weeks in 27 | 6 (4-8)<br>4 weeks in 50<br>6 weeks in 21<br>8 weeks in 41<br>12 weeks in 2 | 8 (4-12)<br>4 weeks in 45<br>6 weeks in 21<br>8 weeks in 40<br>12 weeks in 3<br>No drug in 5 | 8 (4-12)<br>4 weeks in 39<br>6 weeks in 25<br>8 weeks in 38<br>No drug in 12 |
| **Dosage of CAN (mg kg$^{-1}$)** | 2-4 mg kg$^{-1}$ | 2-4 mg kg$^{-1}$ | 2-4 mg kg$^{-1}$ | 2-4 mg kg$^{-1}$ | 2-4 mg kg$^{-1}$ | 2-4 mg kg$^{-1}$ | 2-4 mg kg$^{-1}$ |
| **Number of patients that had attacks** | NA | 0 | 2 | 1 | 5 | 4 | 2 |
| **Number of patients requiring a higher CAN dose or shortening of the dose interval** | NA | 0 | 2 (recurrent attacks) | 0 | 2 (recurrent attacks) | 4 (recurrent attacks) (shortened from 8 to 6 weeks | 2 (recurrent attacks, CAN was restarted) |
| **Number of patients with an extended CAN dose interval** | NA | 0 | 7 patients (prolonged from 4 to 8 weeks)<br>21 patients (prolonged from 4 to 6 weeks) | 16 patients (prolonged from 4 to 8 weeks)<br>2 patients (prolonged from 8 to 12 weeks) | 5 patients (prolonged from 4 to 8 weeks)<br>1 patient (prolonged from 8 to 12 weeks) | 6 patients (prolonged from 4 to 8 weeks) | NA |
| **Number of patients in whom CAN was withdrawn** | 0 | 0 | 0 | 0 | 5 patients | 7 patients | 0 |
| **Number of infections** | NA | 1 (pneumonia) | 1 (upper respiratory tract infection) | 0 | 0 | 0 | 2 (upper respiratory tract infection) |
| **Number of adverse events** | NA | 0 | 0 | 0 | 0 | 0 | 0 |

*Data expressed as median (range).

Furthermore, 5 (4.4%) patients had a positive family history of amyloidosis and renal failure.

All patients had irregular attacks, with a median frequency of 14.5 (range: 2–48) per year. The median attack duration was 3 d (range: 1–14 d). The most common symptom was fever (100%), followed by abdominal pain (n=109 [95.6%]) and chest pain (n=41 [36%]). The most common mutation was M694V/M694V (n=64 [56.1%]) (Table I).

*Treatment response and drug reactions*

At the time of CAN initiation, all the patients were receiving colchicine, with a median dose of 1.5 mg d$^{-1}$ (range: 0.5–2 mg d$^{-1}$), as follows: 0.5 mg d$^{-1}$: n=3; 0.5–1 mg d$^{-1}$: n=37: 1.5 mg d$^{-1}$: n=38: 2 mg d$^{-1}$: n=36. Prior to initiation of CAN, 49 (42.9%) patients were treated with other biologic drugs, as follows: anakinra: n=45; tocilizumab: n=2; etanercept: n=2. Anakinra was switched to CAN in all cases due to local skin reactions or inadequate compliance with daily use. The other biologics were switched to CAN due to the persistence of FMF attacks. The median age at initiation of CAN treatment was 132 months (range: 26–199 months). The median time from diagnosis to initiation of CAN was 64.5 months (range: 36-88 months). CAN was initiated at a subcutaneous dose of 2–4 mg kg$^{-1}$ every 4 or 8 weeks. In all, 94 (82.4%) patients were initially treated with CAN 2 mg kg$^{-1}$ every 4 weeks and the remaining 20 (17.6%) patients received CAN 4 mg kg$^{-1}$ every 8 weeks.

After 1 month of treatment the PGA score, and C-reactive protein (CRP) and serum amyloid A (SAA) levels were significantly lower in all patients ($p$=0.001) (Fig. 1). Neither the dose interval nor CAN dose were changed during the first month of treatment. After 3 months of treatment 2 patients still suffered from recurrent attacks and the CAN dose was increased from 2 mg kg$^{-1}$ to 4 mg kg$^{-1}$. The dose interval was extended in 28 patients after the 3rd month of treatment and after the 6th month no attacks were observed in these 28 patients. In addition, in the 28 patients with an extended CAN dose interval the median PGA score was 0 (range: 0–1) and their CRP and SAA levels were normal. Among the remaining 86 patients, 1 had a mild attack that resolving in 2 d without medication. None of the patients required a higher CAN dose or a reduction in the dose interval. The CAN dose interval was extended in an additional 18 patients after the 6th month of treatment. After the 12th month of CAN treatment, no at-

tacks were observed in 46 patients with an extended dose interval; their median PGA score was 0 (range: 0–1) and their CRP and SAA levels were normal. The CAN dose interval was prolonged in 6 more patients after the 12th month of treatment. After the 18th month of CAN treatment, 4 patients with an extended dose interval had recurrent attacks; all were receiving CAN every 8 weeks. These 4 patients had their CAN dose interval reduced to 6 weeks. After the 24th month of CAN treatment 2 patients that had CAN withdrawn had recurrent attacks, and again began receiving CAN (Table II).

The amyloidosis, family history of amyloidosis, and exertional leg pain rates were higher in the patients that received CAN every 4 weeks than in those that received CAN every 8 weeks, but the differences were not significant (Table III). Erysipelas-like erythema was more common in the patients treated with CAN every 4 weeks. Furthermore, patients treated with a CAN dose interval of 4 weeks had attacks more frequently, whereas as the duration of attacks did not differ according to the CAN dose or interval. There weren't any significant differences in APRs or the PGA score in these group at the time CAN was initiated. All patients that had amyloidosis or a family history of amyloidosis received CAN every 4 weeks (Table III).

During follow-up, patients that received CAN every 8 weeks did not have elevated APRs between attacks, and 12 of the patients were able to have CAN withdrawn, whereas 35 that received CAN every 4 weeks intermittently had elevated APRs during follow-up. The 12 patients that had CAN withdrawn were receiving it every 8 weeks. At baseline they had a lower PGA score (7 *vs*. 8 [*p*=0.840) and CRP level (13.4 *vs*. 18.8 [*p*=0.08]) than the other patients; however, these differences were not significant. Nonetheless, it should be noted that there is a significant numerical difference between the 2 groups.

In brief, during the 24-month follow-up period the CAN dose interval was not changed in 44 patients, of which 4 had amyloidosis and 5 had a family history of amyloidosis; the remaining 35 patients intermittently had elevated APRs during follow-up. The CAN dose interval was extended in 58 patients a median 6 months (range: 3–18 months) after initiation. Among these 58 patients, 4 had a new attack and their dose interval was reduced from 8 weeks to 6 weeks. Lastly, CAN was withdrawn in 12 patients (in 5 after the 12th month of treatment and in 7 after the 18th month). Among these 12 patients, 2 had a new attack within 3 months of withdrawal of CAN and they again received CAN every 8 weeks. The remaining 10 pa-

**Table III.** Comparison of patients with a 4-week CAN dose interval, *versus* an 8-week dose interval.

| | Patients with 4-week dose interval (n=94) | Patients with 8-week dose interval (n=20) | *p* |
|---|---|---|---|
| Clinical findings | | | |
| Fever, n (%) | 94 (109) | 20 (100) | NA |
| Abdominal pain, n (%) | 90 (95.7) | 19 (95) | 1.00 |
| Chest pain, n (%) | 34 (36.1) | 7 (35) | 0.92 |
| Arthralgia, n (%) | 63 (67) | 13 (65) | 0.86 |
| Arthritis, n (%) | 37 (39.3) | 8 (40) | 0.95 |
| Exertional leg pain, n (%) | 38 (40.4) | 4 (20) | 0.08 |
| Prolonged febrile myalgia, n (%) | 4 (4.2) | 0 (0) | 1.00 |
| Erysipelas-like erythema, n (%) | 45 (47.9) | 2 (10) | 0.002 |
| Splenomegaly, n (%) | 14 (14.8) | 2 (10) | 0.73 |
| Amyloidosis n (%) | 4 (4.2) | 0 (0) | 1.00 |
| Pericarditis n (%) | 1 (1) | 0 (0) | 1.00 |
| Frequency of attacks, per year* | 15 (10-48) | 12 (2-24) | 0.01 |
| Duration of attacks, d* | 3 (1-14) | 3 (1-17) | 0.87 |
| **Laboratory findings** | | | |
| CRP, mg $dL^{-1}$** (normal: ≤0.5) | 47 (21-83) | 45 (11-58) | 0.92 |
| ESR, mm $h^{-1}$** (normal range: 0-20) | 48 (33-126) | 46 (3-88) | 0.94 |
| SAA, mg $L^{-1}$** (normal range: <7) | 100 (11-1870) | 88 (2.9-988) | 0.84 |
| **Patient global assessment*** | 8 (6-10) | 8 (5-9) | 0.87 |

*Values given as median (range).
**During an attack before initiation of colchicine.

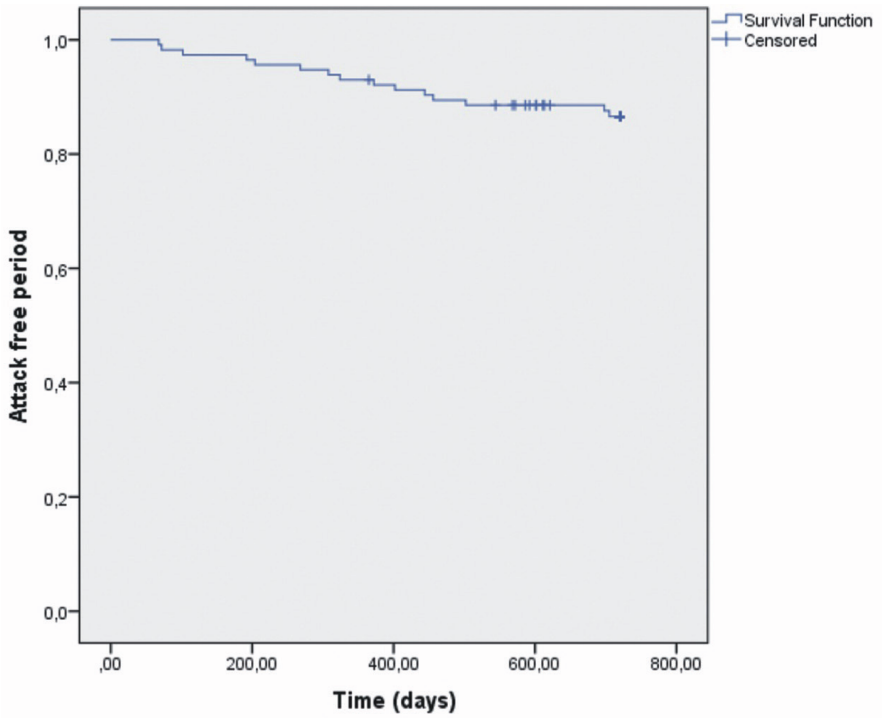


**Fig. 2.** The attack-free period in the crFMF patients treated with CAN.

tients did not report any symptoms at the 24th month follow-up. The median attack-free period under CAN treatment was 669 d (95% CI: 644–696) (Fig. 2).

During the 2736 person-months of follow-up none of the patients had a serious drug reaction. The adverse event rate was 4 mild infections per 228 patient years. In total, 1073 subcutaneous treatments were administered and only 4 patients needed to delay a CAN dose due to mild infection, without requiring hospitalisation (Table II).

## Discussion

The present retrospective observational study assessed the drug survival of CAN in a large paediatric crFMF cohort. The present findings show that CAN is a safe and effective treatment in children with crFMF. Additionally, extending the CAN dose interval leads to recurrence of attacks only in a minority of patients, which can be controlled by returning to the previous dose interval.

The effectiveness of CAN in crFMF patients is supported by 3 clinical trials. Initially, the efficacy of CAN was shown in 7 children with crFMF by a 6-month open-label pilot study (8). The 7 children received CAN 2 mg $kg^{-1}$ every 4 weeks. In total, 6 of the patients met the primary outcome measure of a 50% reduction in attack frequency and 3 of the patients did not have any attacks during the treatment phase. Following the last CAN injection, 5 of the patients had an attack within 25 d (range: 5–34 d). Subsequently, another open-label trial confirmed the effectiveness of CAN in 9 patients with crFMF (11). All 9 patients achieved a ≥50% reduction in attack frequency; however, 5 of the patients had an attack within 71 d (range: 31–78 d) after the last CAN injection. Finally, a randomised control study (CLUSTER trial) reported the effectiveness of CAN in 63 patients with crFMF (12). At baseline all the patients were treated with CAN every 4 weeks for 16 weeks. At week 16 significantly more of the treated patients achieved a clinical response, as compared to those that received a placebo (61% *vs*. 6%). After week 16 the CAN dose interval was extended to 8 weeks and 46% of the crFMF patients maintained their remission. More recently, the long-term (72 weeks) outcomes of the CLUSTER trial were published (18). During the 72-week period 58.3% of the patients had no attacks and 28.3% of the patients had only 1 attack. The safety of CAN was also confirmed by the just-mentioned clinical trials (8, 11, 12). The most common side effect of CAN was mild infections and severe adverse events were rarely observed (8, 11, 12). In addition to clinical studies, the safety and effectiveness of CAN in crFMF patients were reported by many observational studies (13, 19-24), but it remains unclear what are the optimal duration of treatment and dose interval. Eroglu *et al*. (13) reported that the CAN dose interval in 3 of 9 crFMF patients was 12–16 weeks and that in another 3 of the 9 patients CAN was administered on demand; however, their data on drug survival and outcomes in the patients with an extended dose interval were insufficient. Sag *et al*. (21) reported that they extended the CAN dose interval from bimonthly to every 3 months in patients that had complete remission for ≥6 months. In all, 4 of the patients were treated every 3 months, but they provided no data on the outcomes in these patients.

Gul (25) suggested that autoinflammation has 2 dynamic stages, as follows: hyperinflammatory and autonomous. FMF is an autoinflammatory disease that usually presents with self-limited attacks without ongoing inflammation between these "hyperinflammatory" episodes. Nevertheless, some patients may develop sustained inflammation, defined as the "autonomous" production of IL-1β that leads to colchicine resistance. Resetting the autonomous inflammatory state with IL-1 blocking might terminate the ongoing inflammation in crFMF patients (25). A case series supporting this hypothesis was recently published. Akarcan *et al*. (14) reported their standardised CAN protocol in 9 patients with crFMF. According to their protocol, CAN was administered monthly to all patients for 6 months as "initial treatment". Afterward, 3 doses of CAN were administered every 8 weeks as "maintenance treatment". After 9 doses, CAN was withdrawn and all patients were monitored for development of new attacks. In the presence of a new attack CAN was restarted with a dose interval of 12 weeks as "continuation treatment". In all, 4 patients had a new attack within 9 months of the 9$^{th}$ dose of CAN. These 4 children were treated with CAN as "continuation treatment". Even though the aforementioned study offered a standardised protocol, it included a small number of patients.

Real-life data may not always square with standard protocols. FMF is an endemic disease in Turkey and many factors can influence a clinician's treatment approach. In the present study clinicians abstained from extending the CAN dose interval in the presence of intermittently elevated APRs or amyloidosis. Furthermore, in some selected patients CAN may be administered every 8 weeks. In the present study 20 patients were treated with CAN every 8 weeks. Patients that were treated with CAN every 4 weeks had a higher rate of amyloidosis, a family history of amyloidosis, and exertional leg pain, and higher attack frequency, but the differences were not significant.

Although CAN is safe and effective in crFMF patients, clinicians should keep in mind that it is expensive. In the present study the CAN dose interval was extended in 58 patients a median 6 months (range: 3–18 months) after initiation. Among these 58 patients, 4 had a new attack, and then the dose interval was decreased. Moreover, CAN was successfully withdrawn in 12 patients (in 5 after the 12$^{th}$ month of treatment and in 7 after the 18$^{th}$ month). Among these 12 patients, 2 had a new attack within 3 months and they were again administered CAN every 8 weeks. The remaining 10 patients did not report any symptoms at the 24$^{th}$ month follow-up. The present findings show that with careful follow-up the CAN dose interval could be extended in >50% of the patients and that CAN could be withdrawn in 10% of the patients. Furthermore, the safety of CAN was confirmed via 228 patient-years of follow-up.

To the best of our knowledge the present study is the largest to report real-life data on CAN treatment in paediatric crFMF patients. Based on the present findings, we think that as the quantity of real-life data increases, standard CAN protocols may be developed. Recently, a modified Delphi study suggested that in patients without any attacks or laboratory evidence of subclinical inflammation within 6 months of initiation of biologics the CAN dose interval can be doubled and in the absence of any new attacks within 1 year the dose interval can be tripled (5). Based on these suggestions, the same group of researchers are presently conducting a prospective study.

The primary limitations of the present study are its retrospective design and lack of a standard protocol for withdrawal of CAN. This was a collaborative observational that study that included patients from 7 hospitals, and each hospital's approach to extending the CAN dose interval varied. Although FMF is a monogenic disease, it is well-known that its course can vary according to patient; therefore, the treatment approach should be individualised for each patient, which might account for the differences in the approach to treatment between the 7 contributing hospitals. Although patients in the present study were follow-up for 24-months, but longer-term studies are needed.

In conclusion, the present findings show that withdrawal of CAN or extending the dose intervals can be feasible in paediatric crFMF patients. As the quantity of relevant real-life data increases, clinicians may be able to devise standardised tapering strategies for CAN in paediatric crFMF patients.

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